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(54) **Prodrogues glycosylées, leur procédé de préparation et leurs utilisations**

Glykosylierte Arzneimittel-Vorstufen, Verfahren zu ihrer Herstellung und ihre Verwendungen

Glycosylated prodrugs, process for their preparation and uses thereof

(84) Etats contractants désignés:
**AT BE CH DE DK ES FR GB GR IT LI LU NL PT SE**

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(56) Documents cités
**EP-A- 0 410 366**

EP 0 511 917 B1

produkt 4-Nitrophenyl-2-(2,3 4,6-tetra-O-acetyl-α-D-galactopyranosyl)-5-nitrobenzylcarbonat der Formel 47 einsetzt

72. Verfahren zur Herstellung nach einem der Ansprüche 1 bis 27, dadurch **gekennzeichnet**, daß man als Zwischenprodukt 4-Nitrophenyl-2-((2,3,4-tri-O-acetyl-β-D-glucopyranosyl)methyluronat)-5-nitrobenzylcarbonat der Formel 53 einsetzt

73. Verfahren zur Herstellung nach einem der Ansprüche 1 bis 27, dadurch **gekennzeichnet**, daß man als Zwischenprodukt 4-Nitrophenyl-4-methoxy-5-nitro-2-((2,3,4-tri-O-acetyl-β-D-glucopyranosyl)methyluronat)benzylcarbonat der Formel 67 einsetzt.

74. Verfahren zur Herstellung nach einem der Ansprüche 1 bis 27, dadurch **gekennzeichnet**, daß man als Zwischenprodukt 4-Nitrophenyl-4-(2,3,4-tri-O-acetyl-β-D-glucopyranosyl)methyluronat)-5-nitrobenzylcarbonat der Formel 69 einsetzt

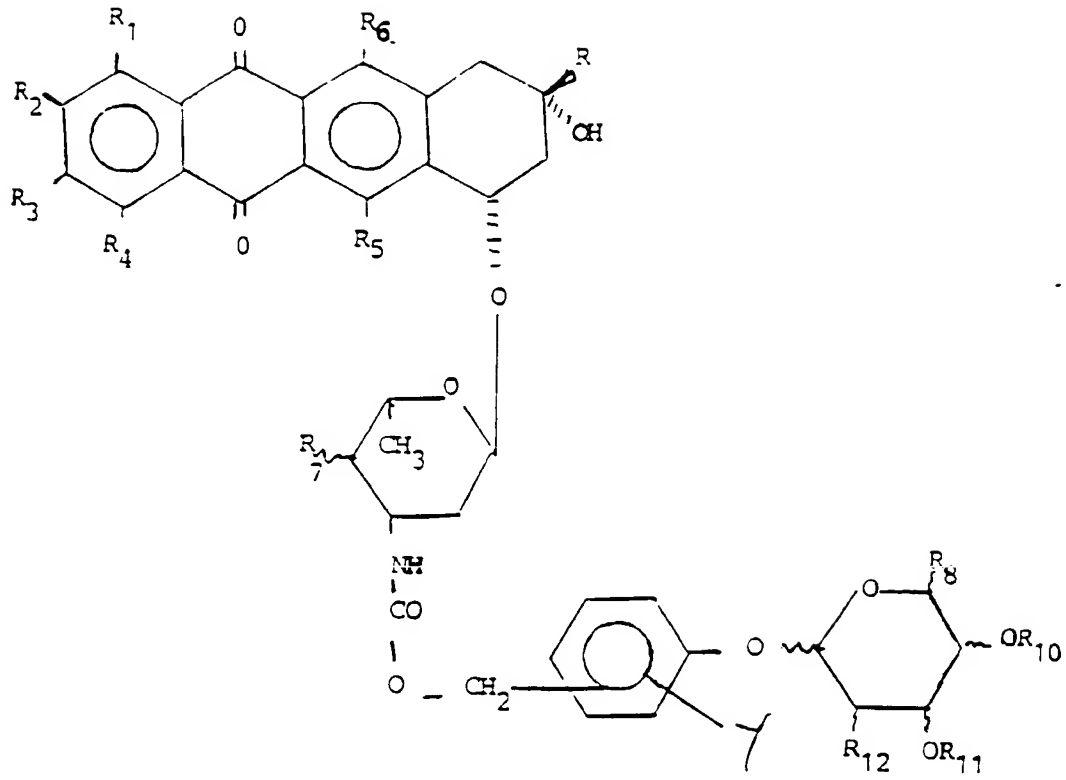
75. Verfahren zur Herstellung nach einem der Ansprüche 1 bis 27, dadurch **gekennzeichnet**, daß man als Zwischenprodukt 4-Chlorphenyl-2-((2,3,4-tri-O-acetyl-β-D-glucopyranosyl)methyluronat)-5-nitrobenzylcarbonat der Formel 81 einsetzt

76. Verfahren zur Herstellung eines Arzneimittels zur Behandlung von Krankheiten, an denen aktivierte Makrophagen, aktivierte Granulozyten, aktivierte Thrombozyten oder aktivierte Tumorzellen beteiligt sind, dadurch **gekennzeichnet**, daß man eine Arzneimittelvorstufe nach einem der Ansprüche 1 bis 27 einsetzt.

## Claims

**Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, PT, SE**

1. An anthracycline prodrug, characterized in that it has formula I below:



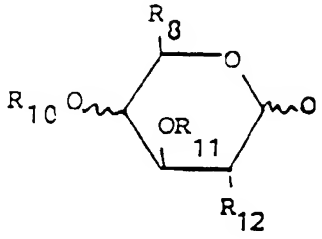
in which

$R_1$, $R_2$ and $R_3$, which can be identical or different, are a hydrogen atom or a hydroxyl group;
$R_4$ is a hydrogen atom, a hydroxyl group or a methoxy group;
R is a group $CO\text{-}CH_2\text{-}R''$, in which R" is a hydrogen atom, a $C_1$-$C_6$ alkyl group, a hydroxyl group, an alkoxy group, an O-acyl group or an aryl group;
$R_5$ and $R_6$, which can be identical or different, are a hydrogen atom or a hydroxyl group;
$R_7$ is a hydrogen atom or a hydroxyl group;
$R_8$ is a group $-CH_2\text{-}OR_9$ or a group $COOR_9$, where $R_9$ is a $C_1$-$C_3$ alkyl or a hydrogen atom;
$R_{10}$ and $R_{11}$ are a hydrogen atom, an acyl protecting group or an alkyl group;
$R_{12}$ is a hydroxyl group, an amine group, an amide group or an O-acyl protecting group;
the benzyl $-CH_2$ is preferably in the para or ortho position to the glycosyl oxygen; and
Y is a hydrogen atom, or at least one electron-attracting group selected especially from the group comprising the $NO_2$ group, a halogen atom and a group $SO_2X$ (where $X = -CH_3$, $C_6H_4\text{-}CH_3$, $NH_2$, $N\text{-}(C_1\text{-}C_4\ alkyl)_2$ or $NH\text{-}C_1\text{-}C_4$ alkyl), -CN, acyl or COO-alkyl, and/or at least one electron-donating group selected from the group comprising groups of the type O-alkyl, NHCO- alkyl, N(alkyl)CO-alkyl, S-alkyl or alkyl.

2. A prodrug according to Claim 1, characterized in that when Y is one or more electron-attracting groups, these are preferably in the ortho and/or para position to the glycosyl oxygen, and when Y is one or more electron-donating groups, these are preferably in the meta position.

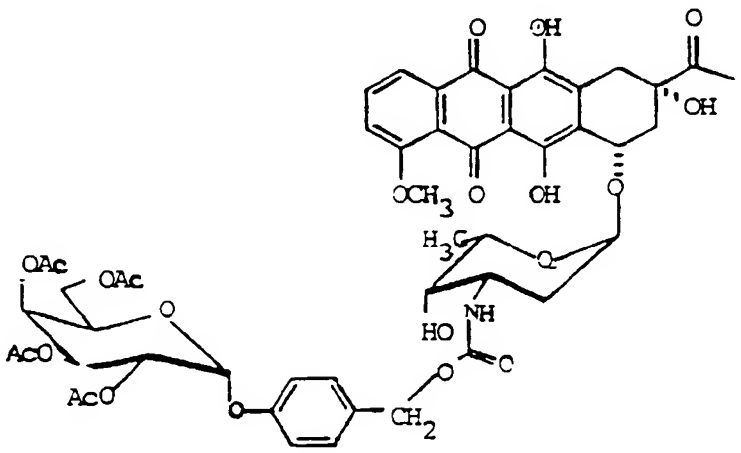
3. A prodrug according to Claim 1 or Claim 2, characterized in that the preferred compounds of formula I contain the

$R_5$ and $R_6$ are hydroxyl groups,
R is a $-CO-CH_3$ group or a $-CO-CH_2OH$ group,
$R_7$ is a hydrogen atom or a hydroxyl group,
$R_8$ is a $-CH_2-OAc$, $-CH_2OH$, -COOMe or -COOH group,
$R_{10}$ and $R_{11}$, which can be identical or different, are a hydrogen atom or an Ac group,
$R_{12}$ is a hydroxyl group or an OAc group,
said radicals $R_8$, $R_{10}$, $R_{11}$ and $R_{12}$ preferably being in the following positions:



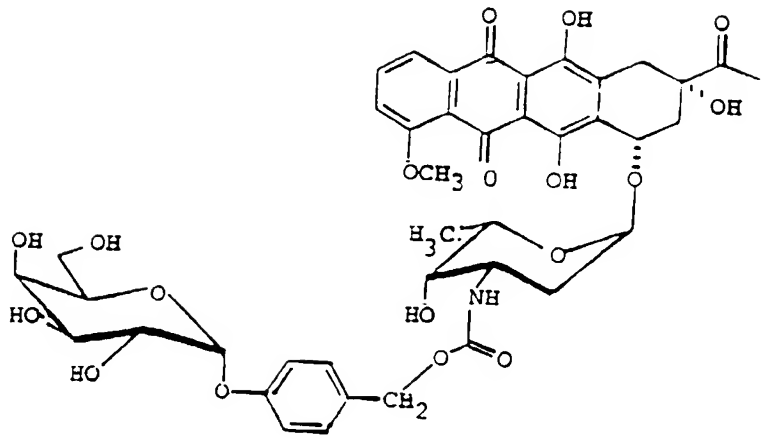
and
Y is a hydrogen atom, an $NO_2$ group or a chlorine atom in the para or ortho position to the glycosyl oxygen, and/or an $OCH_3$ group in the meta position to the glycosyl oxygen.

**4.** A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 6 below:



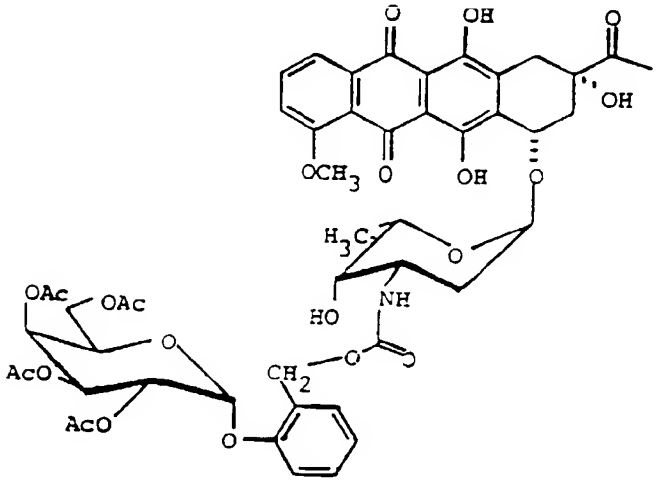
(6)

**5.** A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 7 below:



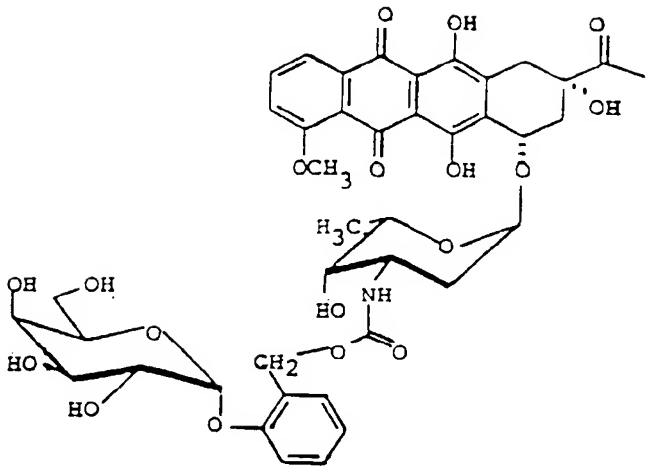
(7)

6. A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 13 below:



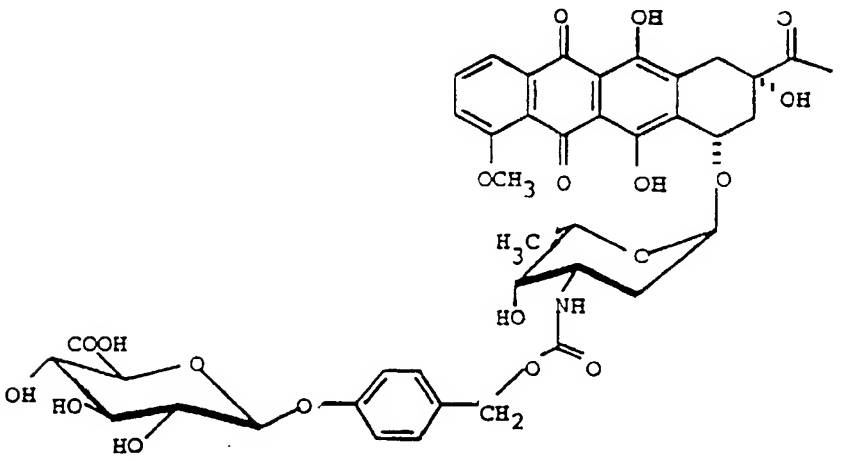
(13)

7. A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 14 below:



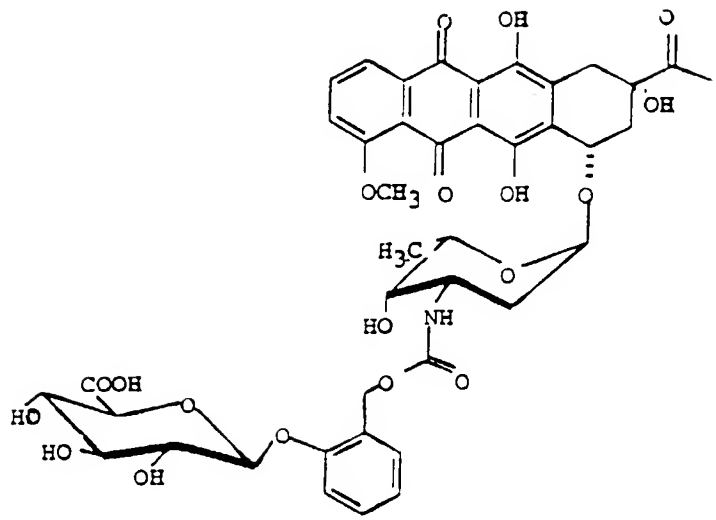
(14)

8. A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 22 below:



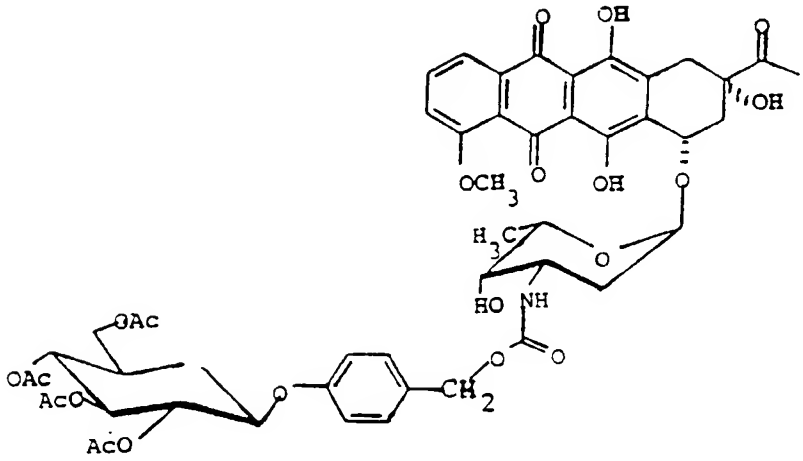
(22)

9. A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 27c below:



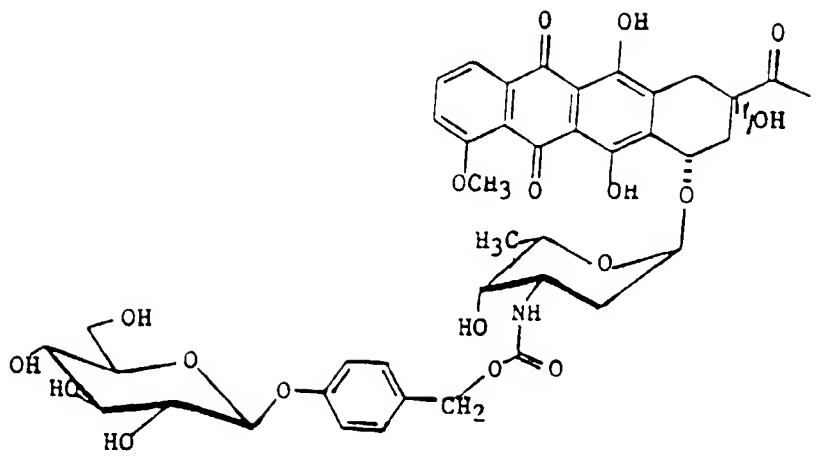
(27c)

10. A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 36 below:



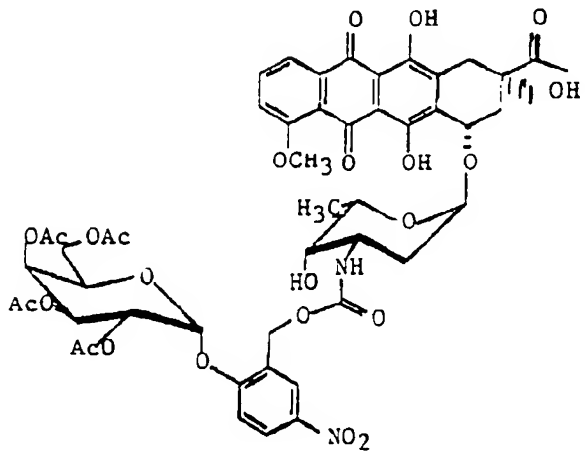
(36)

11. A prodrug according to any one of Claims 1 to 3 characterized in that it has formula 37 below



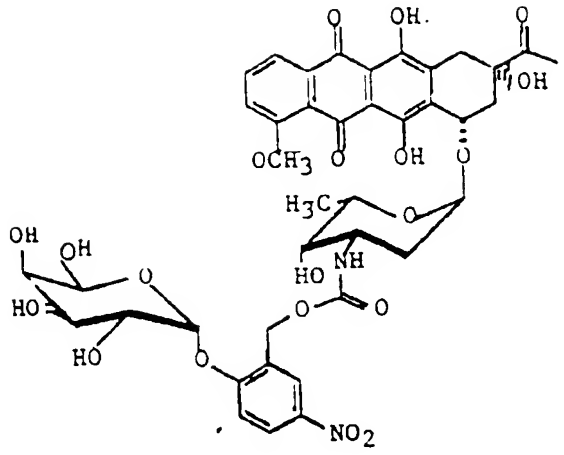
(37)

12. A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 48a below:



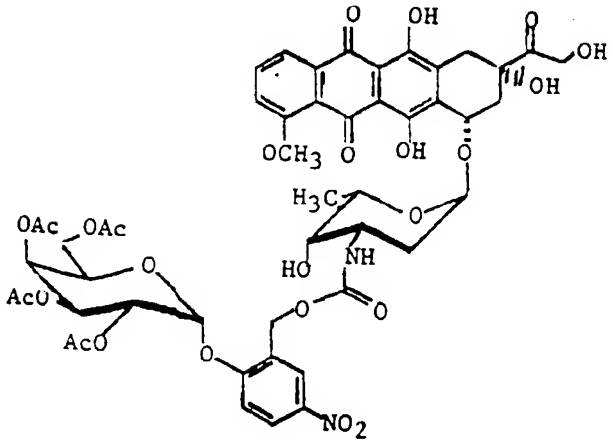
(48a)

13. A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 48b below:



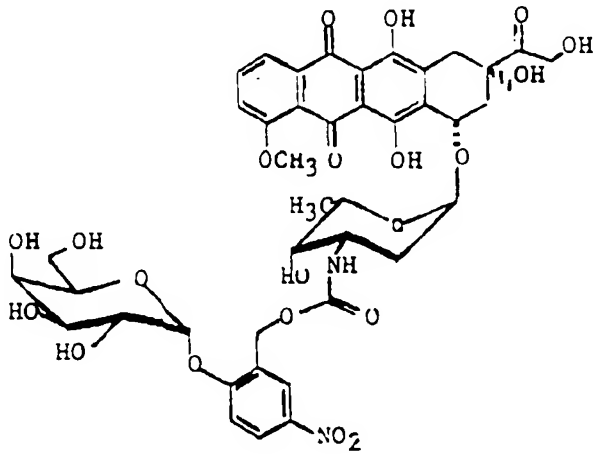
(48b)

**14.** A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 49a below:



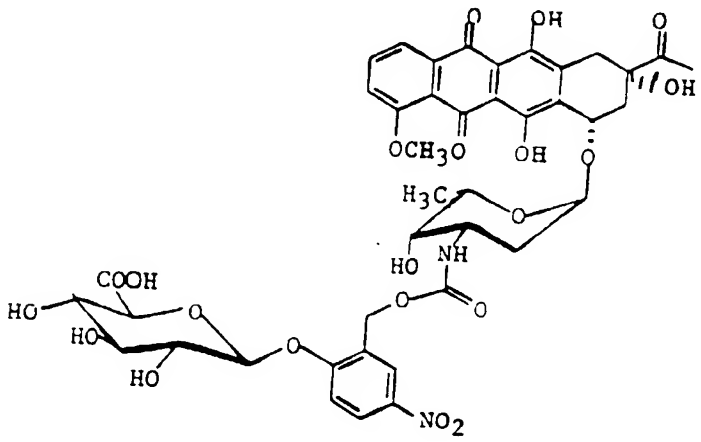
(49a)

**15.** A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 49b below:



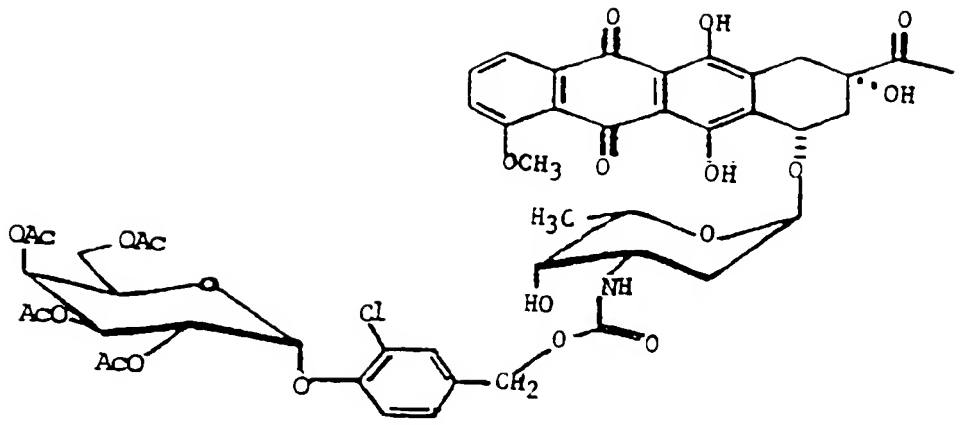
(49b)

**16.** A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 54c below:



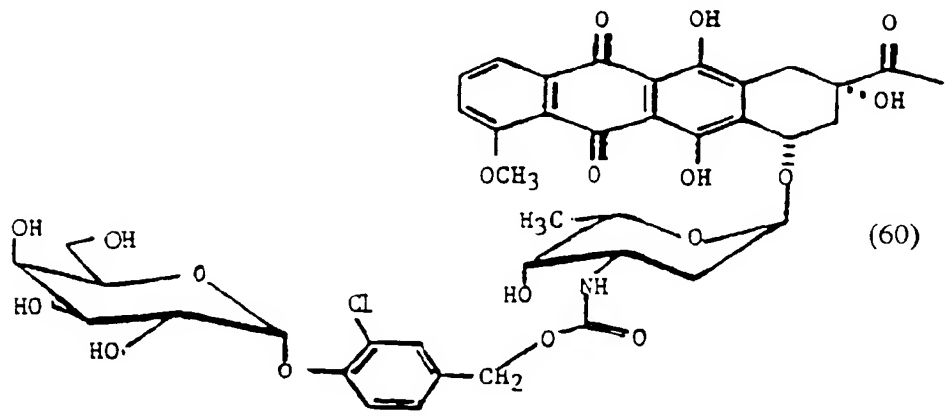
(54c)

**17.** A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 59 below



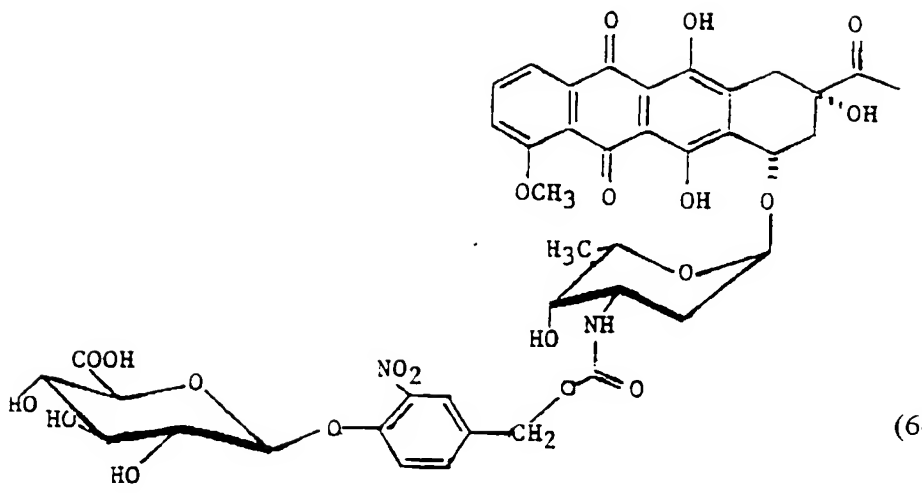
(59)

18. A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 60 below:



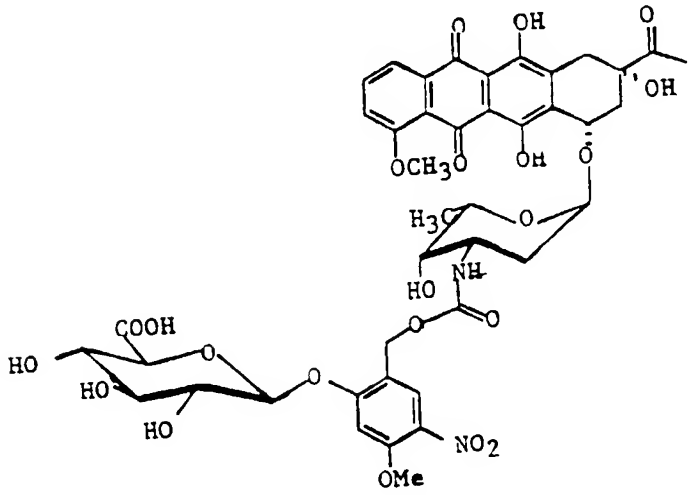
(60)

19. A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 64c:



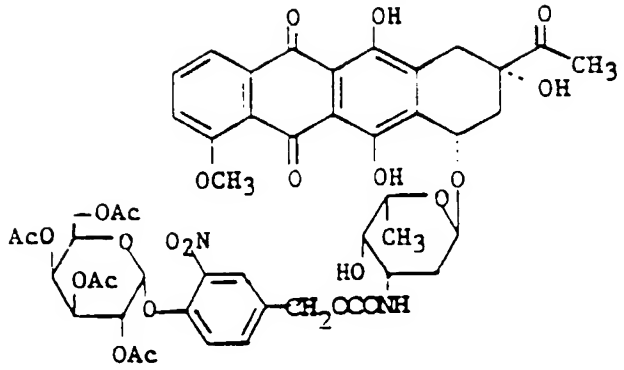
(64c)

**20.** A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 68c below:



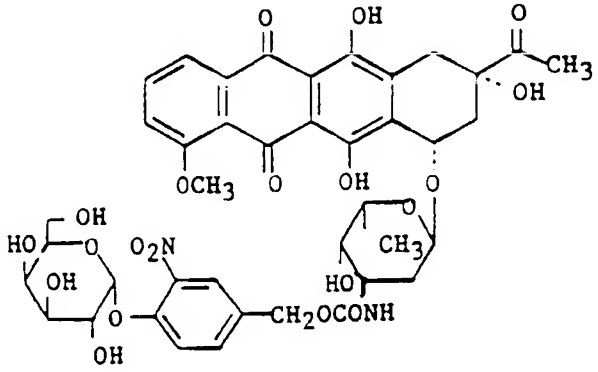
(68c)

**21.** A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 75a below:



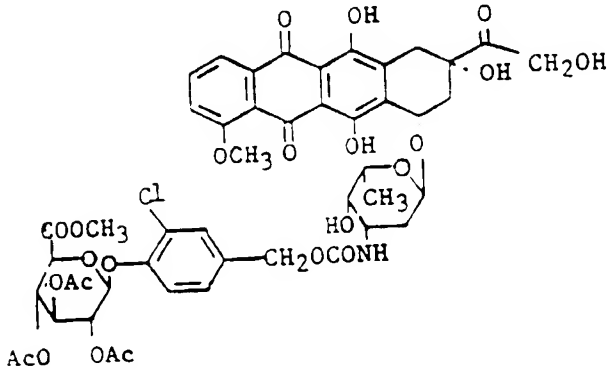
(75a)

**22.** A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 75b below:

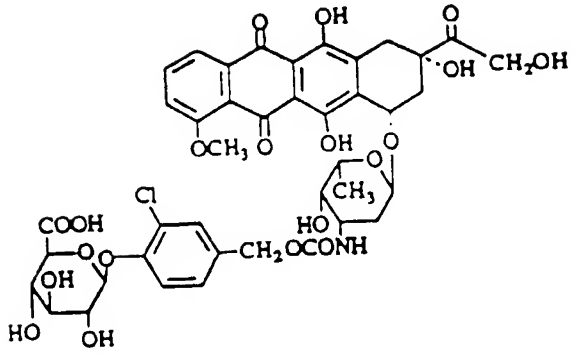


(75b)

**23.** A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 78a below:

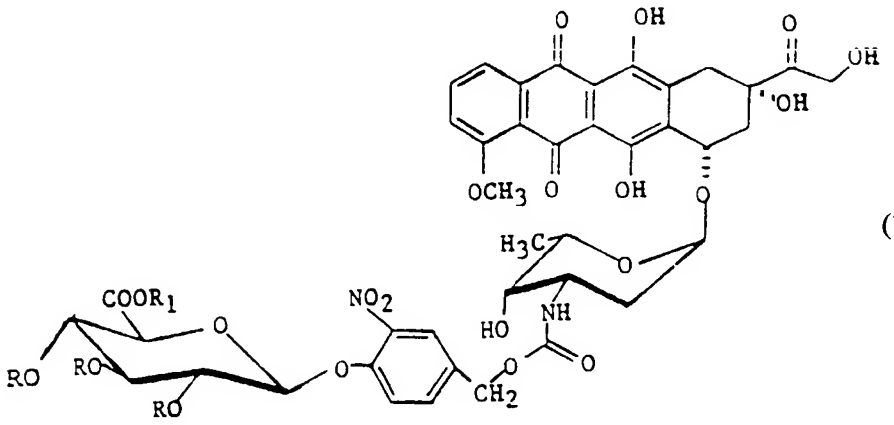


(78a)



(78b)

**25.** A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 70c below:

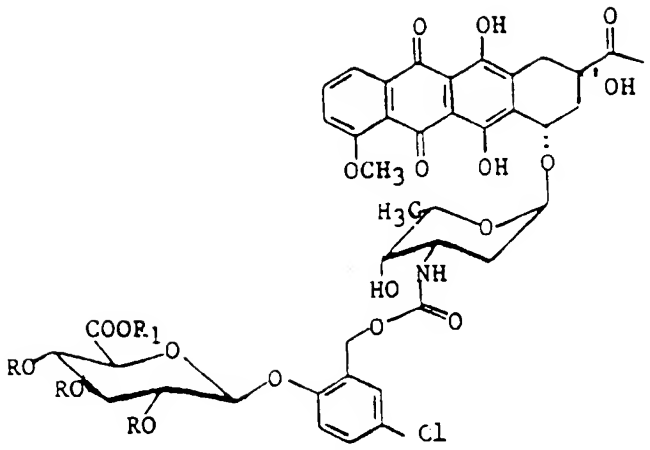


(70)

with:

70a: R=Ac $R_1$=$CH_3$
70b: R=H $R_1$=$CH_3$
70c: R=$R_1$=H

**26.** A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 82 below:

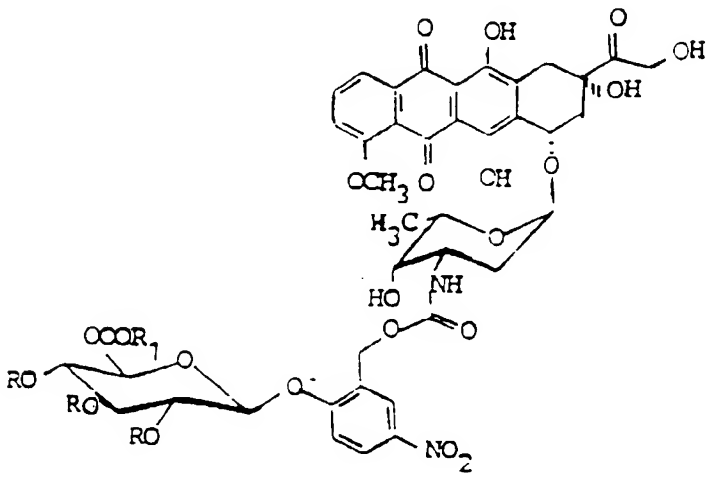


(82)

with:

82a : R=Ac, $R_1$=$CH_3$
82b : R=H, $R_1$=$CH_3$
82c : R=$R_1$=H

**27.** A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 83 below:

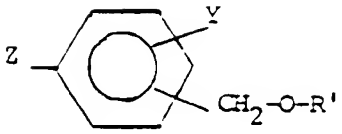


(83)

with

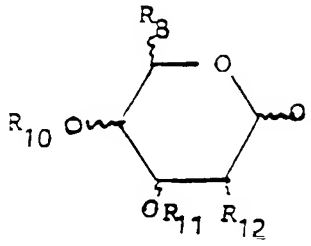
83a : R=Ac $R_1$=$CH_3$
83b : R=H, $R_1$=$CH_3$
83c : R=$R_1$=H

**28.** A method of preparing a compound of formula I, which in particular can be degraded by a glycosidase, characterized in that it comprises

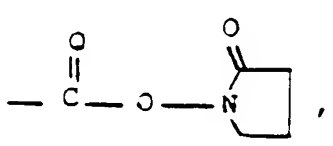


(A)

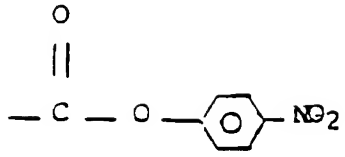
in which
Z is a hydroxyl group, an O-trialkylsilyl group or a group



in which $R_8$, $R_{10}$, $R_{11}$ and $R_{12}$ are as defined above;
R' is one of the following groups:



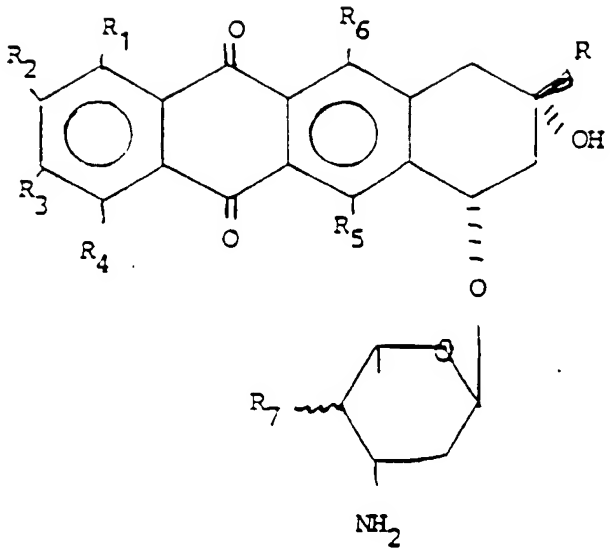
,



the benzyl $-CH_2$ is preferably in the para or ortho position to the phenol group, which may be modified (glycosylated or silylated); and

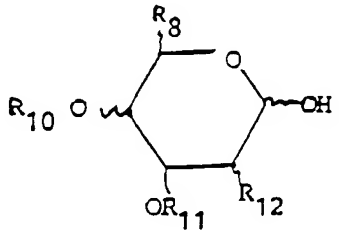
Y is a hydrogen atom, or at least one electron-attracting group selected especially from the group comprising the $NO_2$ group, a halogen atom and a group $SO_2X$ (where X = $-CH_3$, $C_6H_4-CH_3$, $NH_2$, N-($C_1$-$C_4$ alkyl)$_2$ or NH-$C_1$-$C_4$alkyl), -CN, acyl or COO-alkyl, and/or at least one electron-donating group selected from the group comprising groups of the type O-alkyl, NH-CO-alkyl, N(alkyl)CO-alkyl, S-alkyl or alkyl,

with an anthracycline of formula B:



(B)

in which $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$ and R are as defined above;
(2) the removal of the protecting groups present in the compounds obtained, especially by hydrolysis, transesterification or saponification; and
(3) if appropriate, suitable condensation with an ose of the following formula:



in the case where Z is a hydroxyl group or an O-tri-alkylsilyl group, to give an anthracycline prodrug of formula I, in which all the radicals $R_1$ to $R_{12}$ and R are as defined above.

**29.** A method according to Claim 28, characterized in that, prior to step (1), the glycosylated p-hydroxybenzyl derivative is obtained by:

(a) fusion of a cresol with an ose or a peracetylated methyl glucuronate
(b) benzyl bromination of the product obtained.
(c) solvolysis of the brominated derivative, and
(d) activation of the hydroxyl group with a hydroxysuccinimidyl or paranitrophenoxycarbonyl derivative

**30.** Products comprising a modified anthracycline prodrug according to any one of Claims 1 to 27, and an enzyme/tumour-specific antibody conjugate of formula II:

Ab-Sp-E (II)

biomolecule which tends to accumulate in a tumour, such as EGF (epidermal growth factor). α-TGF (α transforming growth factor). PDGF (platelet derived growth factor), IGF I+II (insulin growth factor I+II) or FGF a+b (fibroblast growth factor a+b),

E is a glycosidase which is not immunogenic or has a very low immunogenicity, preferably a mammalian glycosidase such as α-or β-glucosidase, α-galactosidase, α- or β-mannosidase, α-fucosidase, N- acetyl-α-galactosaminidase, N-acetyl-β-/N-acetyl-α-glucosaminidase or β-glucuronidase, and

Sp (arm) is a group containing a sulphide or a disulphide, of formula III or IV:

$$X'(S)_nY' \quad (III)$$

$$X'(S)_n \quad (IV)$$

or a polypeptide arm, in which

X' or Y' is -CO-$R_{13}$-(N-succinimido)- or -C(=$R_{14}$)-$CH_2$-$CH_2$-, where $R_{13}$ is a -$CH_2$-$CH_2$, 1,4-cyclohexylidene, 1,3- or 1,4-phenylene or methoxycarbonyl- or chloro- 1,4-phenylene group and $R_{14}$ is an oxygen atom or an NH group,

Y' represents -C(=$R_{14}$)-$CH_2$-$CH_2$ when $R_{14}$ is as defined above, and

n is 1 or 2,

for use in cytostatic therapy, either simultaneously, separately or spread out over a period of time.

**31.** 4-Bromomethylphenyl 2,3,4,6-tetra-O-acetyl-α-D-galactopyranoside of formula 2, an intermediate in the method according to Claim 28.

**32.** 4-Formylphenyl 2,3,4,6-tetra-O-acetyl-α-D-galactopyranoside of formula 3, an intermediate in the method according to Claim 28.

**33.** 4-Hydroxymethylphenyl 2,3,4,6-tetra-O-acetyl-α-D-galactopyranoside of formula 4, an intermediate in the method according to Claim 28.

**34.** 2-Bromomethylphenyl 2,3,4,6-tetra-O-acetyl-α-D-galactopyranoside of formula 9, an intermediate in the method according to Claim 28.

**35.** 2-Formylphenyl 2,3,4,6-tetra-O-acetyl-α-D-galactopyranoside of formula 10, an intermediate in the method according to Claim 28.

**36.** 2-Hydroxymethylphenyl 2,3,4,6-tetra-O-acetyl-α-D-galactopyranoside of formula 11, an intermediate in the method according to Claim 28.

**37.** Methyl (4-bromomethylphenyl 2,3,4-tri-O-acetyl-β-D-glucopyranoside)uronate of formula 16, an intermediate in the method according to Claim 28.

**38.** Methyl (4-formylphenyl 2,3,4-tri-O-acetyl-β-D-glucopyranoside)uronate of formula 17, an intermediate in the method according to Claim 28.

**39.** Methyl (4-hydroxymethylphenyl 2,3,4-tri-O-acetyl-β-D-glucopyranoside)uronate of formula 18, an intermediate in the method according to Claim 28.

**40.** Methyl (2-bromomethylphenyl 2,3,4-tri-O-acetyl-β-D-glucopyranoside)uronate of formula 23, an intermediate in the method according to Claim 28.

**41.** Methyl (2-hydroxymethylphenyl 2,3,4-tri-O-acetyl-β-D-glucopyranoside)uronate of formula 24, an intermediate in

od according to Claim 28.

**43.** 2-Tert-butyldimethylsilyloxybenzaldehyde of formula 28, an intermediate in the method according to Claim 28.

**44.** 2-Tert-butyldimethylsilyloxybenzyl alcohol of formula 29, an intermediate in the method according to Claim 28.

**45.** N-[2-Hydroxybenzyloxycarbonyl]daunorubicin of formula 32, an intermediate in the method according to Claim 28.

**46.** 4-Formylphenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside of formula 33, an intermediate in the method according to Claim 28.

**47.** 4-Hydroxymethylphenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside of formula 34, an intermediate in the method according to Claim 28.

**48.** N-[4-Hydroxybenzyloxycarbonyl]daunorubicin of formula 38, an intermediate in the method according to Claim 28.

**49.** 2-Methyl-4-nitrophenyl 2,3,4,6-tetra-O-acetyl-α-D- galactopyranoside of formula 42, an intermediate in the method according to Claim 28.

**50.** 2-Bromomethyl-4-nitrophenyl 2,3,4,6-tetra-O-acetyl-α-D-galactopyranoside of formula 43, an intermediate in the method according to Claim 28.

**51.** 2-Dibromomethyl-4-nitrophenyl 2,3,4,6-tetra-O-acetyl-α-D-galactopyranoside of formula 44, an intermediate in the method according to Claim 28.

**52.** 2-Formyl-4-nitrophenyl 2,3,4,6-tetra-O-acetyl-α-D- galactopyranoside of formula 45, an intermediate in the method according to Claim 28.

**53.** 2-Hydroxymethyl-4-nitrophenyl 2,3,4,6-tetra-O-acetyl-α-D-galactopyranoside of formula 46, an intermediate in the method according to Claim 28.

**54.** Methyl (2-formyl-4-nitrophenyl 2,3,4-tri-O-acetyl-β-D-glucopyranoside)uronate of formula 51, an intermediate in the method according to Claim 28.

**55.** Methyl (2-hydroxymethyl-4-nitrophenyl 2,3,4-tri-O- acetyl-β-D-glucopyranoside)uronate of formula 52, an intermediate in the method according to Claim 28.

**56.** 2-Chloro-4-methylphenyl 2,3,4,6-tetra-O-acetyl-α-D- galactopyranoside of formula 55, an intermediate in the method according to Claim 28.

**57.** 2-Chloro-4-bromomethylphenyl 2,3,4,6-tetra-O-acetyl-α-D-galactopyranoside of formula 56, an intermediate in the method according to Claim 28.

**58.** 2-Chloro-4-hydroxymethylphenyl 2,3,4,6-tetra-O-acetyl-α-D-galactopyranoside of formula 57, an intermediate in the method according to Claim 28.

**59.** Methyl (4-formyl-2-nitrophenyl 2,3,4-tri-O-acetyl-β-D-glucopyranoside)uronate of formula 61, an intermediate in the method according to Claim 28.

**60.** Methyl (4-hydroxymethyl-2-nitrophenyl 2,3,4-tri-O-acetyl-β-D-glucopyranoside)uronate of formula 62, an intermediate in the method according to Claim 28.

**61.** (4-bromomethyl 2-nitro)-phenyl 2,3,4 6-tetra-O-acetyl-α-D-galactopyranoside of formula 73, an intermediate in the method according to claim 28.

63. 4-hydroxy-3-chlorobenzaldehyde 2,3,4-tri-O-acetyl-β-D-methylglucuronide of formula 76, an intermediate in the method according to claim 28.

64. (4-hydroxy-methyl-2-chloro)-phenyl 2,3,4-tri-O-acetyl-β-D-methylglucuronide of formula 77, an intermediate in the method according to claim 28.

65. 2,5-Dioxopyrrolidin-1-yl 4-(2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl)benzyl carbonate of formula 5, an intermediate in the method according to Claim 28.

66. 2,5-Dioxopyrrolidin-1-yl 2-(2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl)benzyl carbonate of formula 12, an intermediate in the method according to Claim 28.

67. 2,5-Dioxopyrrolidin-1-yl 4-(methyl (2,3,4-tri-O-acetyl-β-D-glucopyranosyl)uronate)benzyl carbonate of formula 19, an intermediate in the method according to Claim 28.

68. 4-Nitrophenyl 2-(methyl (2,3,4-tri-O-acetyl-β-D-glucopyranosyl)uronate)benzyl carbonate of formula 26, an intermediate in the method according to Claim 28.

69. 4-Nitrophenyl 2-(tert-butyldimethylsilyloxy)benzyl carbonate of formula 30, an intermediate in the method according to Claim 28.

70. 2,5-Dioxopyrrolidin-1-yl 4-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)benzyl carbonate of formula 35, an intermediate in the method according to Claim 28.

71. 2,5-Dioxopyrrolidin-1-yl 4-dimethyl-t-hexylsilyloxybenzyl carbonate of formula 40, an intermediate in the method according to Claim 28.

72. 4-Nitrophenyl 2-(2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl)-5-nitrobenzyl carbonate of formula 47, an intermediate in the method according to Claim 28.

73. 4-Nitrophenyl 2-(methyl (2,3,4-tri-O-acetyl-β-D-glucopyranosyl)uronate)-5-nitrobenzyl carbonate of formula 53, an intermediate in the method according to Claim 28.

74. 4-Nitrophenyl 4-methoxy-5-nitro-2-(methyl (2,3,4-tri-O-acetyl-β-D-glucopyranosyl)uronate)benzyl carbonate of formula 67, an intermediate in the method according to Claim 28.

75. 4-Nitro-phenyl 4-(methyl (2,3,4-tri-O-acetyl-β-glucopyranosyl) uronate)-5-nitro-benzyl carbonate of formula 69, an intermediate in the method according to claim 28.

76. 4-chlorophenyl 2-(methyl (2,3,4-tri-O-acetyl-β-D-glucopyranosyl) uronate)-5-nitrobenzyl carbonate of formula 81, an intermediate in the method according to claim 28.

77. Application of the prodrugs according to claims 1 to 27 to the preparation of drugs for the treatment of diseases, which involve activated macrophages, granulocytes, thrombocytes or human tumoural cells

**Claims for the following Contracting States : ES, GR**

1. A method of preparing anthracycline prodrugs having the following formula I: